



SYMPOSIUM INTRODUCTION

Chemical Responses to the Biotic and Abiotic Environment by Early Diverging Metazoans Revealed in the Post-Genomic Age

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From the symposium “Chemical responses to the biotic and abiotic environment by early diverging metazoans revealed in the post-genomic age” presented at the annual meeting of the Society for Integrative and Comparative Biology, January 3–7, 2019 at Tampa, Florida.

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Synopsis For many years methodological constraints limited insights on the molecular biology of non-model organisms. However, the development of various sequencing platforms has led to an explosion of transcriptomic and genomic data on non-model systems. As a consequence the molecular drivers of organismal phenotypes are becoming clearer and the chemicals that animals use to detect and respond to their environments are increasingly being revealed—this latter area inspired our symposium theme. The papers in this volume broadly address this theme by their more specific focus in one of the following general areas: 1) sensory biology and the molecular basis of perception, 2) chemicals deployed to deal with the biotic and abiotic environment, and 3) chemical interactions along the parasite–mutualist continuum. Here we outline and synthesize the content of these papers—an exercise which demonstrates that sophisticated gene repertoires enable early diverging metazoans to encode many of the signaling, sensory, defensive, and offensive capacities typically associated with animals that have complex nervous systems. We then consider opportunities and associated challenges that may delay progress in comparative functional biochemistry, a reinvigorated field that can be expected to rapidly expand with new ‘omics data. Future knowledge of chemical adaptations should afford new perspectives on the comparative evolution of chemical mediators.

Introduction

It is increasingly apparent that interactions of organisms with their environment can shape their development and phenotype and that organisms can, in turn, alter their environments (Sultan 2015). Phenotypes can thus arise from a sophisticated orchestration of reciprocal processes involving the animal genome, the holobiome, and environmental interactions. Many interactions with the environment are mediated by chemicals involved with sensory function, for example in perceiving the environment or in recognizing predators, prey, or suitable habitats. Other chemicals may be deployed as effectors. The latter may be used for intimate and potentially long term defensive and offensive interactions with other organisms such as symbionts (including parasites) and hosts. These varying chemical

interactions can entail extensive chemical signaling pathways and molecular cross talk that involve responses implemented by intracellular organelles, cells, glands, tissues, and organs. These interactions are contingent on the specific properties of key molecules.

We are now beginning to comprehend the diversity of such chemically-driven genome–environment interactions thanks to advances in molecular techniques that enable study of non-model systems. In particular, understanding genome structure and gene expression under different environmental conditions is now possible given the low cost and accessibility of whole genome and transcriptome sequencing platforms along with recent technical advances in proteomics and the bioinformatics necessary for analyzing enormous datasets. As a result

there has been an explosion of transcriptomic, genomic, and proteomic data on early diverging metazoans in the past few years.

Extant early-diverging metazoans (Fig. 1) have survived for many millions of years in a changing and increasingly complex world. Molecular clock analyses infer the ancient Neoproterozoic origins of each of these early diverging metazoan lineages (some 900–600 Mya; Dohrmann and Wörheide 2017)—origins that are independently supported, for example, by the fossil cnidarian *Corumbella wermeri* (543 Mya; Van Iten et al. 2014). These extant lineages of early diverging metazoans have survived over time despite the challenges of five mass extinctions and the evolution of morphologically more complex animals (the bilaterians). Furthermore, apart from placozoans, these early diverging metazoans are often diverse, abundant, and ecologically important constituents of marine ecosystems in the present day. In addition, some early-branching metazoans (e.g., sponges and hydrozoans [including the model organism *Hydra*]) have managed to colonize freshwater environments along with bryozoans, molluscs, and crustaceans, although other invertebrate taxa have apparently been constrained to marine environments (e.g., urochordates, echinoderms, scaphopods, brachiopods, phoronids). The cnidarians have also extensively radiated as an endoparasitic clade (the Myxozoa) characterized by complex life cycles and exploitation of marine, freshwater, and terrestrial hosts (Okamura et al. 2015a). What factors may have contributed to the successful persistence and diversification of these early branching animals over long and challenging periods of time involving substantial biotic and abiotic change?

This question impelled us to propose and organize a symposium to consider how early diverging metazoans are able to detect and respond to their environments. Novel insights revealed by –omics data on the diversity of peptides and small molecules deployed by these animals make it increasingly clear that sophisticated gene repertoires enable these animals to encode many of the signaling, sensory, defensive, and offensive capacities typically associated with complex nervous systems. Thus it is timely to consider how environmental and chemical cues may shape phenotypes of early diverging animals. The aim of our symposium was therefore to develop a post-genomic view on the form, functions, and origins of compounds that are biosynthesized in early diverging metazoans in response to environmental cues. Insights on the diversity of such “chemical adaptations” may afford new perspectives on the evolution of chemical mediators in morphologically simple animals, thus

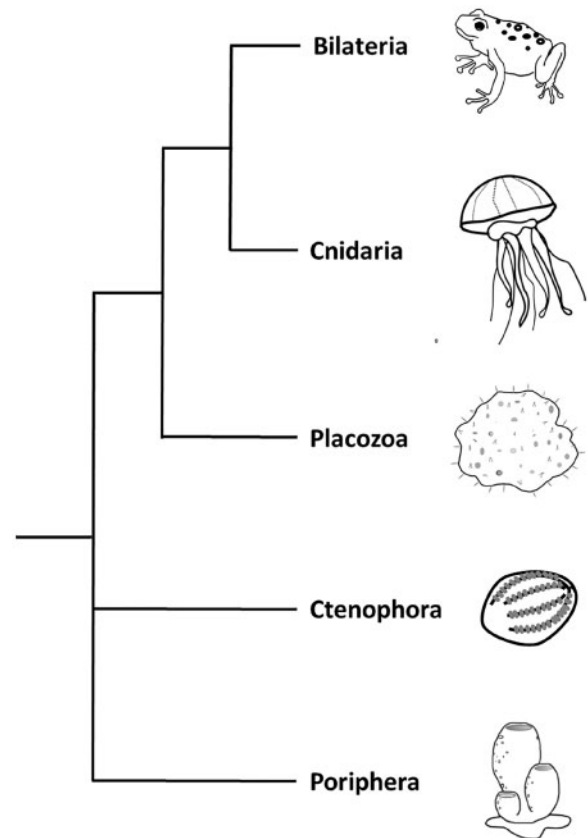


Fig. 1 Phylogenetic tree of early diverging metazoans (based on Sebé-Pedrós et al. 2018), including unresolved relationship of cnidarians+bilaterians with sponges and ctenophores.

contributing to our general knowledge of comparative functional biochemistry.

Below we highlight how papers arising from our symposium provide data and insights relevant to three general areas: 1) sensory biology and the molecular basis of perception, 2) chemicals deployed to deal with the biotic and abiotic environment, and 3) chemical interactions along the parasite–mutualist continuum. We then consider the timeliness and value of post-genomic approaches for understanding how organisms respond to changing environments. This, in turn, leads us to develop a more synthetic view and to consider opportunities and associated challenges that may impede progress in the reinvigorated field of comparative functional biochemistry. We predict that this field will rapidly expand as multiplying –omics data enhance our understanding of the evolution of chemically mediated organism–environment interactions in the animal kingdom.

Information gathering: sensory biology

All animals perceive and respond to environmental signals. In bilaterian animals this is achieved by sophisticated nervous systems. Non-bilaterian animals,

however, may use sensory cells, electrochemical signaling, and, in some cases, nerve nets and rings. In addition, the neural system of ctenophores may be independently derived (Dunn et al. 2008; Moroz et al. 2014). Papers in this volume explore the potential driving role of light-induced stress and associated key stress-related proteins during the initial and subsequent stages in the evolution of photoreception and eyes, and the sensory biology of sponges, which lack a nervous system.

Light sensitivity is foundational for vision and involves key proteins used by animals to sense light. However, explaining the origins and evolution of complex eyes, vision, and photoreception solely on the basis of increasing ability for sensing light is problematic and potentially circular. By reviewing a vast literature, Swafford and Oakley (2019) are able to point out that many proteins used as screening pigments, photosensitive pigments (opsins), and in lenses are linked with reactive oxygen species (ROS) and UV stress responses to light-induced damage. For example opsins are able to mitigate and endure photostress, screening pigments (e.g., melanin) that enable detection of directionality by shading also provide UV protection, and many lens proteins that are concentrated in front of photoreceptors should reduce UV damage and guard against toxins. Swafford and Oakley (2019) therefore propose that light-induced stress, not vision, was the initial impetus and continued to play a major role in the origins and evolution of eyes, vision, and photoreception. In particular, they argue that selection for co-expression and co-regulation of genetic information was required to bring together different components of the eye before selection for visual acuity was effective. Comparative studies are required to test this scenario and it can be anticipated that future 'omics studies will provide data that can be used to inform on the evolution of stress response networks in early branching animals and bilaterians. Such analyses may help to reveal whether co-option or *de novo* evolution is required to explain the evolution of complex traits such as eyes.

The surprisingly sophisticated ways that sponges respond to their environment involve signaling capacities that are effective despite their lack of conventional nerves. Coordinated contractions of sponges are invariably slow and can result from a variety of stimuli. In addition, many sponges display spontaneous periodic contractions over different time periods (reviewed by Leys et al. 2019). Sponge larvae also respond to light (despite lacking opsins) and gravity, and chemical cues are involved in their settlement and metamorphosis. An astonishing

recent observation gained by long term monitoring is that sponges may predict the weather, contracting in response to pressure anomalies in advance of a storm (Leys et al. 2019). This contraction could be adaptive as it will shut down suspension-feeding activities thereby avoiding clogging of the sponge's extensive internal filtering system comprised of choanocyte chambers and anastomosing canals. Contraction may also avoid damage by minimizing exposure to storm-generated drag forces. This response begs the question of what mechanisms sponges use to detect these pressure anomalies and to convey information that achieves an integrated response. In general, although sponges have many cellular receptors the communicating pathways that generate a global response are unknown—one possibility is cumulative responses to the same stimulus. How sponges coordinate their behaviors is an active area of research.

Dealing with the biotic and abiotic environment

Animals must deal with changing conditions in their biotic and abiotic environment that offer opportunities (e.g., feeding) or pose challenges (e.g., defense). Contributions to this volume variously consider how early branching animals react to environmental challenges and opportunities by chemically-mediated responses and adaptations. In some cases the molecular basis for these adaptations is relatively clear while in others they remain a mystery. In many cases the unique chemical compounds employed by early diverging metazoans may have practical applications.

Paul et al. (2019) reviewed the complexity and host specificity of sponge microbiomes and the link between microbial symbionts and chemical defense production. Marine sponges host a staggering diversity of microbial symbionts, and these associations merge the metabolic capabilities of hosts and symbionts, allowing the sponge holobiont to utilize and recycle nutrients that would otherwise be unavailable. These associations are highly species-specific—even closely related sponge species have unique microbiomes. Sponges are also prolific sources of secondary metabolites, and many of these compounds may be produced by microbial symbionts. For example, toxic polybrominated diphenyl ethers produced by filamentous cyanobacteria comprise up to 12% of the dry weight of their sponge hosts. Metagenomic data showing biosynthetic gene clusters involved in the production of toxic compounds within sponge microbiomes (Agarwal et al. 2017), and correlated host-symbiont phylogenies and

metabolomic studies also suggest that microbial symbionts may be mediating the production and diversification of compounds across sponge species. It is therefore likely that microbial symbionts have played a critical role in sponge ecology and evolution by both facilitating access to novel sources of nutrients and producing compounds that allow sponges to compete for space and deter pathogens and predators. Fortunately, the potential for exploiting sponge secondary compounds by the pharmaceutical industry may facilitate further research on the dynamics, maintenance, and control of sponge microbiomes and the role of bacterial associates in the production of defensive compounds in sponges.

Cnidarians are widely recognized to harbor venoms delivered by their cnidocytes for use in prey capture and defense (Morandini et al. 2014) but there has been relatively little investigation of variation in the complex mixture of toxins (comprised of both proteins and peptides) that form their venoms. Do nematocysts convey distinctive venom payloads? Does venom composition vary with environments or phylogeny? Is variation in toxin abundance of biological relevance? Jaimes-Becerra et al. (2019) explored these questions by examining protein families in cnidarians and other venomous animals. Although the abundance of some toxins can be variable, the composition of venom does not vary greatly between nematocyst types or taxonomic class. Application of non-supervised cluster analysis suggests that simple cnidarians produce venoms that are just as complex as those produced by bilaterians. Evidence to date suggests that cnidarians use an array of different nematocyst types to deliver a single venom rather than produce variable venoms. Nematocyst diversity may therefore be important in the interspecific interactions that cnidarians can be expected to encounter in their varied and variable environments.

Many cnidarians and ctenophores inhabit deep-sea environments characterized by high pressure and low temperature. These conditions present a challenge for retaining tertiary structure required for function of biomacromolecules such as proteins and membrane lipids. Selection has therefore enabled proteins to remain appropriately folded in barophiles that tolerate high hydrostatic pressure at depth (Chen and Makhataadze 2017). To determine the structural basis of pressure tolerance, Winnikoff et al. (2019) developed a comparative transcriptome analysis to predict which amino acid sites in a protein are under selection in association with a continuous phenotype or

environmental parameter. This analysis can be applied to countless phenotypes beyond pressure tolerance and may thus be of broad use to comparative protein biochemists. Results of the analysis applied to alignments of metabolic enzymes from ctenophore species spanning a 4000-m depth range illustrate what can be learned by comparing transcriptomes across environmental extremes. This sort of investigation may eventually yield principles for rational design of proteins (Winnikoff et al. 2017). Should comparative transcriptomic predictions be upheld experimentally, then the structural innovations that enabled ctenophores, cnidarians, and sponges to colonize the most disparate niches on Earth may become valuable components of the bioengineer's toolbox.

Oxidative stress is the product of damage to molecules such as proteins, lipids, and nucleic acids caused by ROS. Co-adapted cellular processes that overcame metabolic toxicity resulting from highly reactive molecular oxygen are crucial to aerobic life and have even been suggested to explain the origin of sex in eukaryotes (Hörandl and Speijer 2018). To survive oxidative stress, which is exacerbated by internal organelles, xenobiotics, and UV radiation, a variety of antioxidant compounds and enzymes are used to detoxify reactive intermediates or repair damage. The expression of enzymes that protect against ROS is coordinated by a small number of related nuclear transcription factors. Doonan et al. (2019) explore variation in the use of these transcription factors in cnidarians and other early diverging metazoans by analyzing genomic, transcriptomic, and proteomic datasets. Their comparative genomic and transcriptomic analysis provided evidence that key stress response genes (Nrf2 homologs) evolved early in metazoans, while others (Keap1) appeared later in the last common ancestor of cnidarians and bilaterians. Furthermore, the key Nrf2–Keap1 interacting domains are not conserved within the cnidarian lineage which suggests that this pathway evolved within Bilateria. Nevertheless, the presence of several known downstream target genes of Nrf2 suggests that homologs of Nrf2 play an important role in the oxidative stress response in cnidarians, despite the absence of Keap1. Doonan et al. (2019) refer to these homologs as Nrf to avoid confusion with mammalian Nrf2 proteins. Overall this study provides the first evidence for Nrf-mediated cellular defense by early diverging metazoans to oxidative stress, a response that may have been critical to survival during dramatic changes in the Earth's oxidative environment over time (Gacesa et al. 2016).

Chemical interactions along the parasite–mutualist continuum

Intimate and prolonged symbiotic associations between different organisms are widespread in early diverging metazoans. In sponges and cnidarians these may be particularly promoted by interactions across large surface areas resulting from their relatively simple essentially epithelial level of organization (Okamura et al. 2015b). These large collective surfaces that function in resource capture may facilitate the establishment of intimate relationships with endosymbionts. Symbiotic associations can range from parasitism, where one organism benefits at the expense of the other, to mutualism, where both organisms benefit. In reality there is a dynamic continuum between parasitism and mutualism because positive and negative effects are context-dependent (e.g., Ashby and King 2017). For example, zooxanthellae may positively contribute to coral host nutrition but their uncontrolled growth can decrease calcification and coral growth (Marubini and Davies 1996; Cunning and Baker 2013; Lesser et al. 2013). This parasite–mutualist continuum is further tested when environmental stress is increased, pushing the symbiosis toward parasitic exploitation that may cause a breakdown in certain symbiosis, known as bleaching (Lesser et al. 2013). By its very nature, the establishment of endosymbionts requires avoidance of host immune responses that would normally combat invasion by foreign bodies. In addition the various requirements of both hosts and endosymbionts must be accommodated in enduring endosymbioses. Contributions to this volume that address this general topic include focus on the molecular bases and regulation of immune responses in ctenophores and cnidarians. The paper by Doonan et al. (2019) is also relevant in presenting data pertinent to how free-living and parasitic cnidarians may vary in dealing with oxidative stress.

Various components of the innate immune system are present across life, from single-celled to multicellular organisms (Buchmann 2014). Detection of non-self is mediated by pattern-recognition receptors (PRRs) that recognize pathogen-associated molecular motifs. Such recognition triggers signaling responses that enable binding, engulfing, or killing potential invaders according to canonical pathways involving transcription factors. The innate immune system is the primary pathogen defense system used by invertebrates and may have critically contributed to the origin of multicellularity (Travis 2009). Immune responses of ctenophores, however, have received

little investigation. The nature of ctenophore innate immunity is thus of considerable interest in view of the unclear phylogenetic status of ctenophores as potential sister group to all metazoans (Ryan et al. 2013; Moroz et al. 2014). Traylor-Knowles et al. (2019) provide new insights into the immune repertoire of ctenophores. Scanning genome data for *Mnemiopsis leidyi* and *Pleurobrachia bachei* and transcriptome data for *Hormiphora californiensis* provides evidence for a range of innate immunity genes in ctenophores while experiments using stained bacteria have revealed two possible phagocytic cell types. This work sets the stage to characterize conserved and novel genes involved in ctenophore immune responses and to examine transcriptional changes following pathogen challenge.

The characterization of intracellular PRRs in corals is the focus of the contribution from Dimos et al. (2019). Using bioinformatic tools they were able to probe existing genomes and transcriptomes of the Caribbean reef-building coral *Orbicella faveolata* for its Nod-like receptor (NLR) repertoire. Innate immunity is key to how corals may both overcome disease and increase their tolerance for certain diseases. Therefore understanding the different receptor repertoires in coral species is important. The NLRs are a family of intracellular receptors that can bind to both extracellular threats, like pathogen cell walls, or intracellular threats that arise from cellular dysfunction. Since corals face challenges from diseases and infectious agents, as well as from cellular toxins (e.g., ROS during temperature stress) these receptors are integral to coral immunity. Dimos et al. (2019) detected 46 NLRs in *O. faveolata* and theoretically identified the potential interaction protein partners, including apoptotic inducers and immune activators. This type of synthesis demonstrates the diversity of these important receptors and opens the door to experimental determination of their role in coral immunity.

Another use of bioinformatic data in this post-genomic era is to identify protein sequences from high throughput proteomic data sets. Ricci et al. (2019) adopted this approach to describe an immune response in a diseased gorgonian coral collected from the field. While the pathogen is still unknown, the disease is characterized by noticeable black pigmentation on the surface of the octocoral that originates from cellular melanization. The proteomic data analyzed by Ricci et al. (2019) are layered with transcriptomic data (described in Fuess et al. 2018) from the same samples. One of the shortfalls of transcriptomic studies is lack of knowledge about whether proteins are produced and how this affects the

phenotype. Using proteomics should thus help to interpret transcriptomic data, and in many cases congruence between the proteome and transcriptome is lacking (e.g., Diz et al. 2012). The data presented here are no exception—there were only eight matches between the octocoral proteome and transcriptome. Nevertheless, the proteome revealed some unique immune-related profiles. For example, differences in protein expression between healthy and diseased octocorals were driven by increases in inflammatory and lectin sugar binding proteins and decreases in proteins involved with growth and reproduction in diseased octocorals. Such data layering analyses enabled by genomic resources may provide critical insights on trade-offs and immune responses involved in coral disease.

Weis (2019) reviews how recent progress in understanding coral–dinoflagellate symbiosis has been foundational, promoting knowledge of chemical mediators that initiate, maintain, and disrupt symbiosis. However, this progress is also of concern because the pace of discovery of how symbiosis is generated and maintained is lagging behind the rapid decline of coral reefs due to climate change—a process that might at least be partially addressed if it were possible to reduce dysbiosis and bleaching by informed manipulation. Her review highlights how the sea anemone, *Aiptasia* (*Exaiptasia pallida*) has served as a valuable laboratory model revealing the central role of innate immunity in the health of cnidarian–dinoflagellate symbioses. Consequently there is now overwhelming evidence that innate immunity also plays a critical role in coral–dinoflagellate symbiosis. RNAseq and genome studies routinely provide evidence for a high abundance of innate immunity genes in coral–dinoflagellate symbioses, and it is clear that innate-immunity genes are highly diverse in cnidarians (especially in symbiotic cnidarians) compared with bilaterians (Neubauer et al. 2017). The review of proteins involved in innate immunity provides background evidence for the apparent central role of innate immunity in interpartner regulation associated with three processes: development (including interpartner recognition); maintenance (via dynamic homeostasis); and disruption (dysbiosis and bleaching) of symbiosis. There is growing evidence that dysbiosis and bleaching are driven not only by oxidative stress but by disruption of metabolic homeostasis. Particular challenges in our understanding of coral–dinoflagellate symbiosis are cell cycle dynamics of hosts and symbionts, and the nature of the symbiosome membrane complex and trafficking dynamics. A more complete understanding

based on the cell biology of the partnership could enable future efforts to strategically engineer functional symbiosis to deal with climate change.

In addition to providing evidence for a shared evolutionary history of regulatory pathways involved in the oxidative stress response (see previous section), Doonan et al. (2019) also obtained evidence that genes encoding Nrf2 homologs present in free-living cnidarians may have been independently lost in some parasitic cnidarian (some myxozoans) lineages but not in others (*Polypodium hydriforme* and other myxozoans). While these results may be artifactual (e.g., due to loss of data upstream of assembly or poor coverage) they are also in keeping with loss of genes associated with parasitism. If the latter is true, questions arise as to whether Nrf2-mediated oxidative stress response in certain endoparasitic myxozoans is reduced and, if so, how? Is the host oxidative stress response sufficient to avoid exposure to damaging free radicals? Do parasites export damaging molecules to be dealt with by hosts?

Comparative functional biochemistry: opportunities and challenges

We are only beginning to comprehend the diversity of genome–environment interactions because next generation sequencing and big data science have made ‘omics approaches increasingly affordable, accessible, and user-friendly. As papers in this volume demonstrate, it is clear that early diverging animals have surprisingly sophisticated gene repertoires encoding much of the signaling, sensory, defensive, and offensive capacities of bilaterian animals. Evidence that some signaling employed in the sensory biology of bilaterians has been inherited from non-metazoans (e.g., protists, fungi; Leys et al. 2019) illustrates that phenotypes may arise from traits inherited from ancestors. However, there is growing evidence that the same chemicals may be used for different signaling functions in different groups (e.g., acetylcholine; Leys et al. 2019). In addition, there is also evidence for unique signaling capacities (e.g., in sponges [Leys et al. 2019] and corals [Dimos et al. 2019]), for considerable variation in signaling systems (Leys et al. 2019; Weis 2019) and in the production of effectors (Paul et al. 2019; Ricci et al. 2019). Such effectors can often result from complex chemical interactions in “holobionts” and demonstrate how intimately interacting organisms can work collectively to achieve responses, mediators, and outcomes that may benefit or threaten the functional integrity of the

assembled constituents. As illustrated by Weis (2019) these holobiont systems vividly illustrate how “organismal traits” can thus result from the complex dynamics of multiple intimately-interacting phenotypes.

As a consequence of new technologies and studies such as those presented in this volume, many early diverging metazoans are now promoted within the scientific community as models for genome-level projects. It is thus timely to illustrate how –omics methods can be used to resolve how environmental and chemical cues shape phenotypes in early diverging metazoans and may critically contribute to the continued success of these ancient lineages. Without such understanding we are unlikely to develop effective comparative frameworks for the study of animal evolution nor envision how to deal with impending impacts of climate change. Furthermore, as pointed out for example by Leys et al. (2019) and Swafford and Oakley (2019), our currently biased molecular insights can lead to mistakes in functional attribution and in confirmation bias when reviewing the available literature. Meanwhile, while falling costs of next generation sequencing platforms have made generating vast amounts of sequence data increasingly affordable, the gap between obtaining these sequences and then assigning biological function to them continues to widen. More rapid and higher throughput functional biochemistry methodologies are required if we are to avoid exaggerating conclusions based on sequence data alone.

In summary, the papers arising from our symposium have provided insights on the diversity of chemical interactions that early diverging animals use to deal with their varying biotic and abiotic environments. These interactions contribute to a growing picture of comparative functional biochemistry, revealing how chemical mediators have enabled persistence and diversification of early branching animals over geological time. In future it may be possible to test hypotheses regarding the relative diversities of chemical mediators in early- and later-diverging taxa, the relationship between chemical diversity and morphological complexity, and the evolutionary ecology of players that contribute to holobionts. We can expect this field to flourish with continued developments and improvements in technological and analytical approaches. However, this resurgence will require an integration of expertise in molecular biology, bioinformatics, and organismal biology to ensure appropriate generation and interpretation of data, and, most importantly, to achieve subsequent synthesis and

predictions about patterns and processes in the natural world.

Acknowledgments

The symposium “Chemical response to the abiotic and biotic environment of early diverging metazoans revealed in the post-genomic era” was part of the Society for Integrative and Comparative Biology annual meeting in Tampa in January 2019. The symposium was supported by several SICB divisions (Division of Ecoimmunology and Disease Ecology [DEDE], Division of Neurobiology, Neuroethology, and Sensory Biology [DNNSB], Division of Phylogenetics and Comparative Biology [DPCB]) as well as the American Microscopical Society. The authors would like to acknowledge Ashlie Hartigan for help in drafting Fig. 1.

Funding

This work was supported by the National Science Foundation IOS Award No. 1831860 and the Leverhulme Trust [grant RPG-2016-037].

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